STEM CELLS

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Stem Cells

- Stem cells are unique in that they have the ability to divide and differentiate into specialized cells, making them promising candidates for regenerative medicine
- Medical treatments use stem cells to repair or replace damaged or diseased cells in the body.
- Cells harvested from adipose tissue are well studied and of particular interest given their relative abundance, ease of harvest, and low immunogenicity
- Bone marrow aspirate concentrate has documented evidence in certain patient populations

Stem Cells

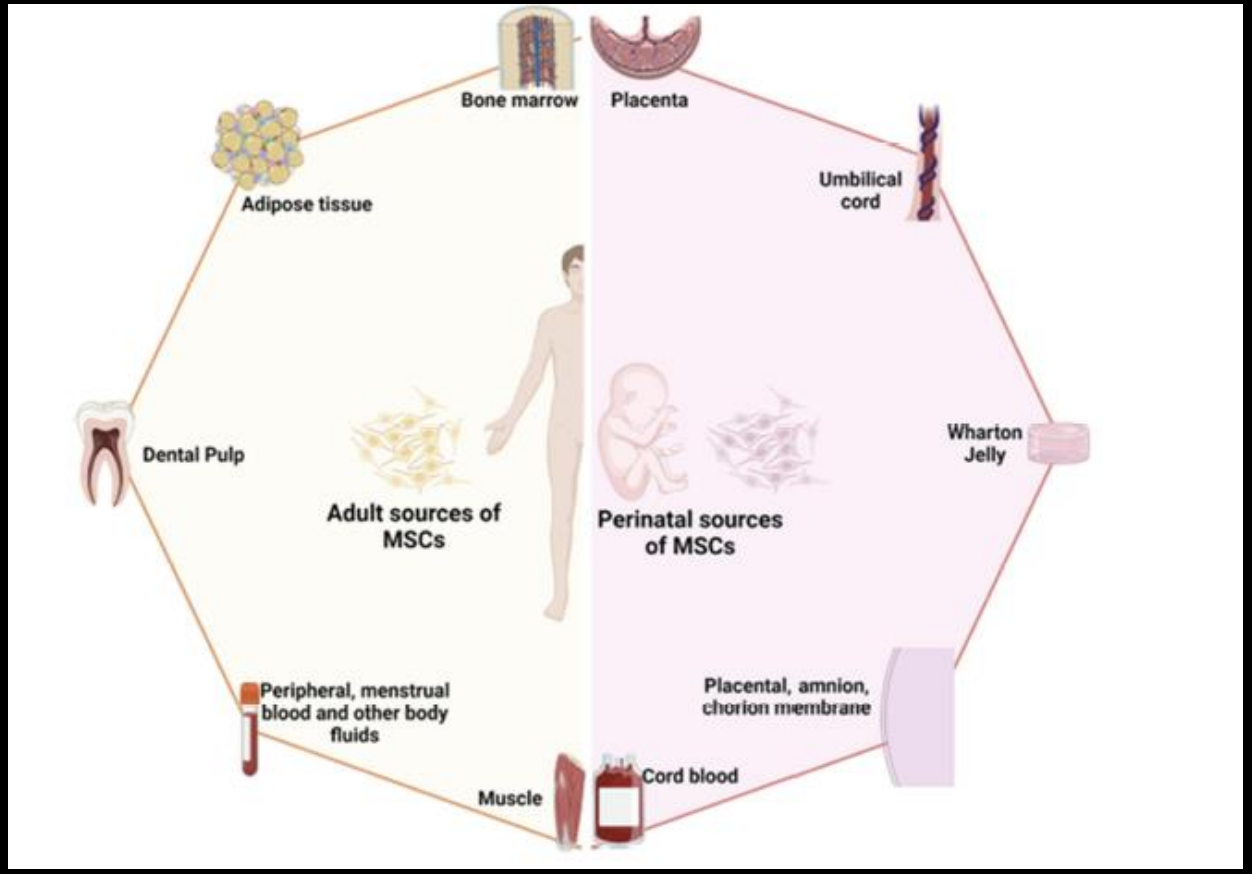
Types of Stem Cell Therapy:

- **Autologous transplant: Stem cells are harvested from the patient's own body.**
- **Allogeneic transplant:** Stem cells are received from a donor.
- **Induced pluripotent stem cell (iPSC) therapy:** Stem cells are created from the patient's own skin cells or other tissues.

Stem Cell Therapy-Indications

Stem cell therapy is currently used to treat a variety of conditions, including:

- Blood cancers (e.g., leukemia, lymphoma)
- Bone marrow disorders
- Immune disorders
- Heart disease
- Diabetes
- Parkinson's disease
- Alzheimer's disease
- Hair Loss
- **Pain/Function**



D'Souza, et al. Journal of Pain Research 2024:17 2951–3001

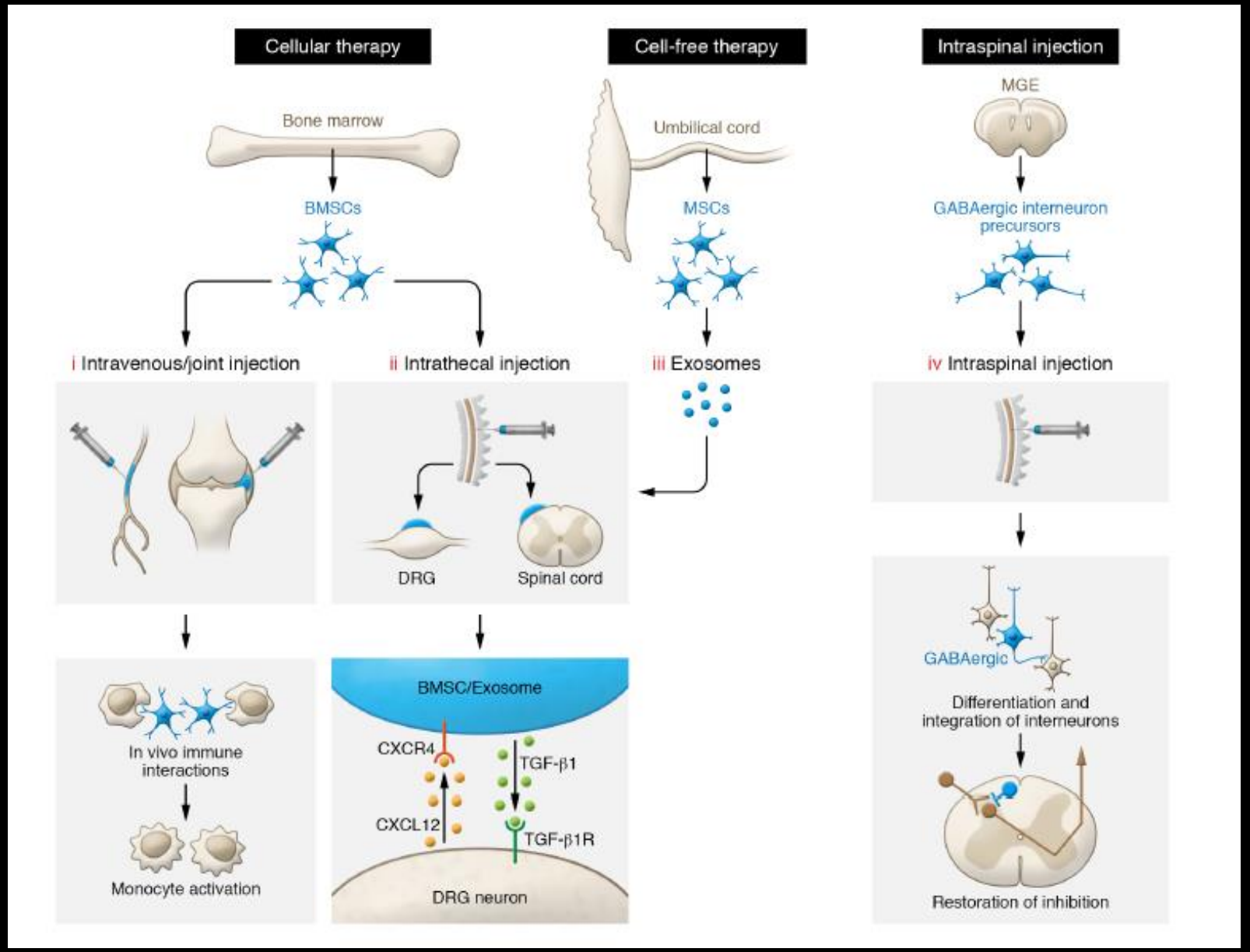
Regenerative therapy is currently used to treat a variety of conditions, including:

- **Pain/Function**
  - **Spine: Disc, Facet, SIJ**
  - **OA Hip/Knee/Shoulder/Foot/Hand**
  - **Tendinitis/Tendinopathy**
    - **Lateral/Medial epicondylitis**
    - **Rotator Cuff**
    - **Achilles**
    - **Plantar Fascia**
    - **Proximal Hamstring/Gluteal**
  - **Muscle Injury/Strain**
  - **Neuropathic Pain**
    - **DPN/SCI/Radiculopathy/Trigeminal Neuralgia/PHN**

What are the important biological components?

Mesenchymal stem cells (MSCs)

- Derived from multiple sources: bone marrow, adipose, and umbilical cord
- The cell lines may differentiate to cartilage, muscle, and bone, given appropriate cell culture media
- Clinically, MSCs often are injected immediately after harvest (non-cultured cells)
- Infused MSCs induce a phenotypic change in circulating macrophages
  - upregulating anabolic and anti-inflammatory cytokines
    - IL10 and TGF-b



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What are the important biological components?

- BMAC stands for Bone Marrow Aspirate Concentrate. It's a non-surgical treatment that uses a patient's own bone marrow to treat joint pain and other conditions.

How it works

- A small sample of bone marrow is extracted from the pelvic bone
- The sample is processed to concentrate the stem cells, growth factors, and anti-inflammatory proteins
- The concentrate is injected into the damaged joint or other structure

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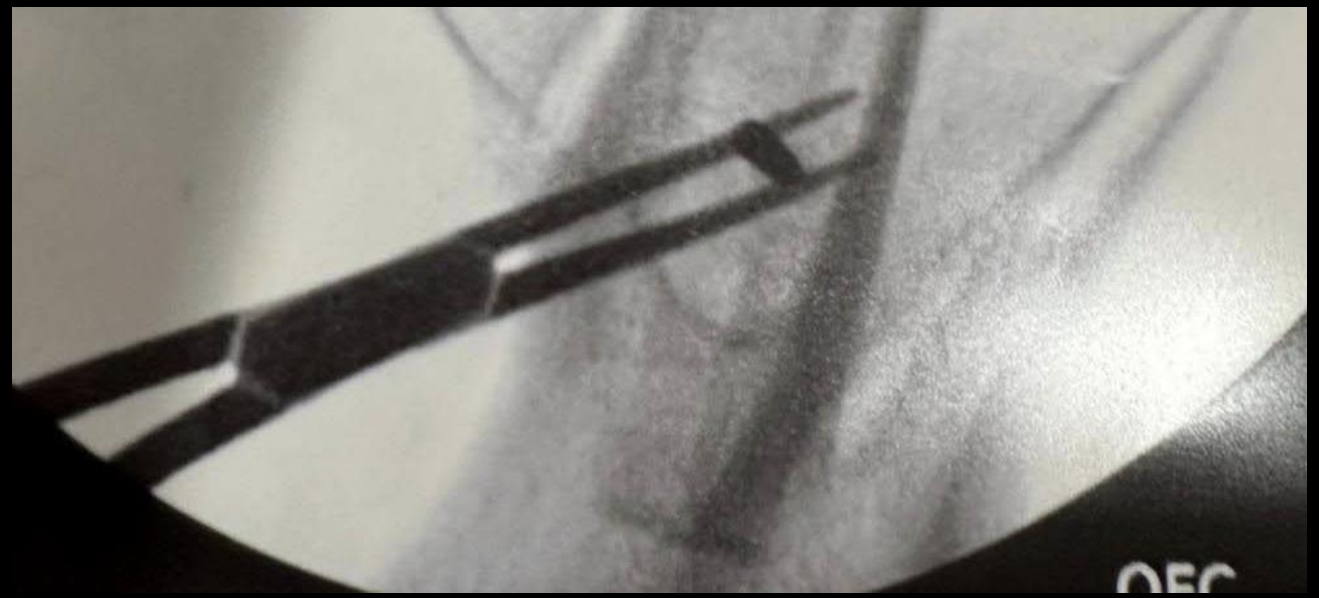
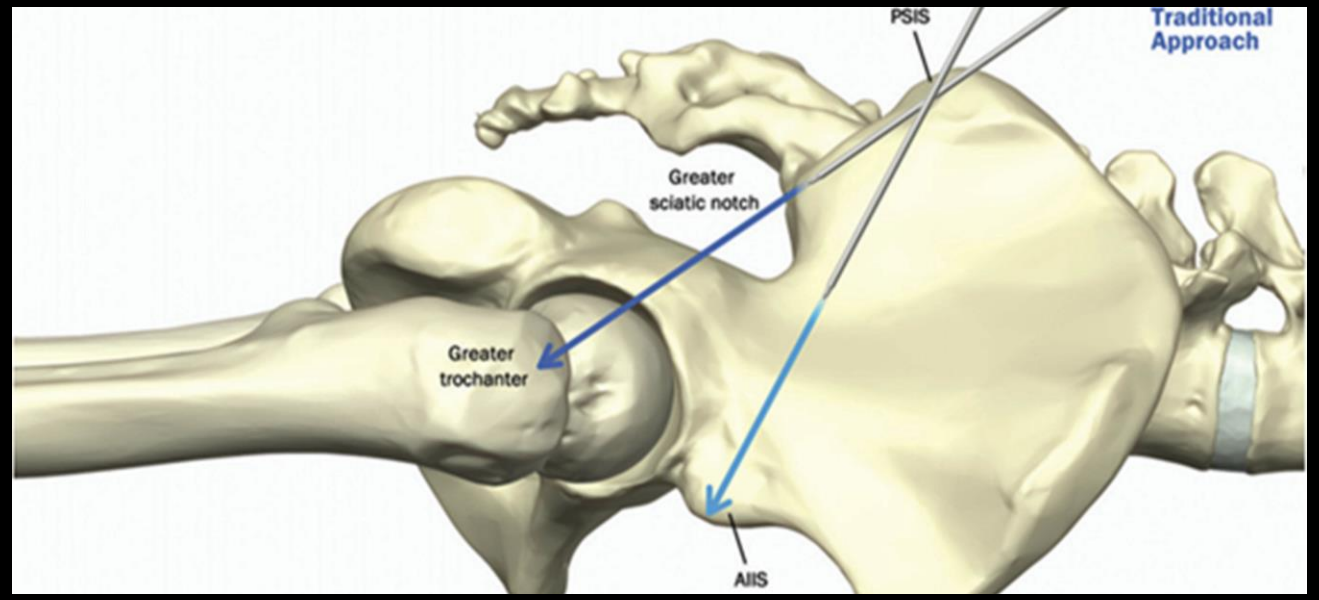


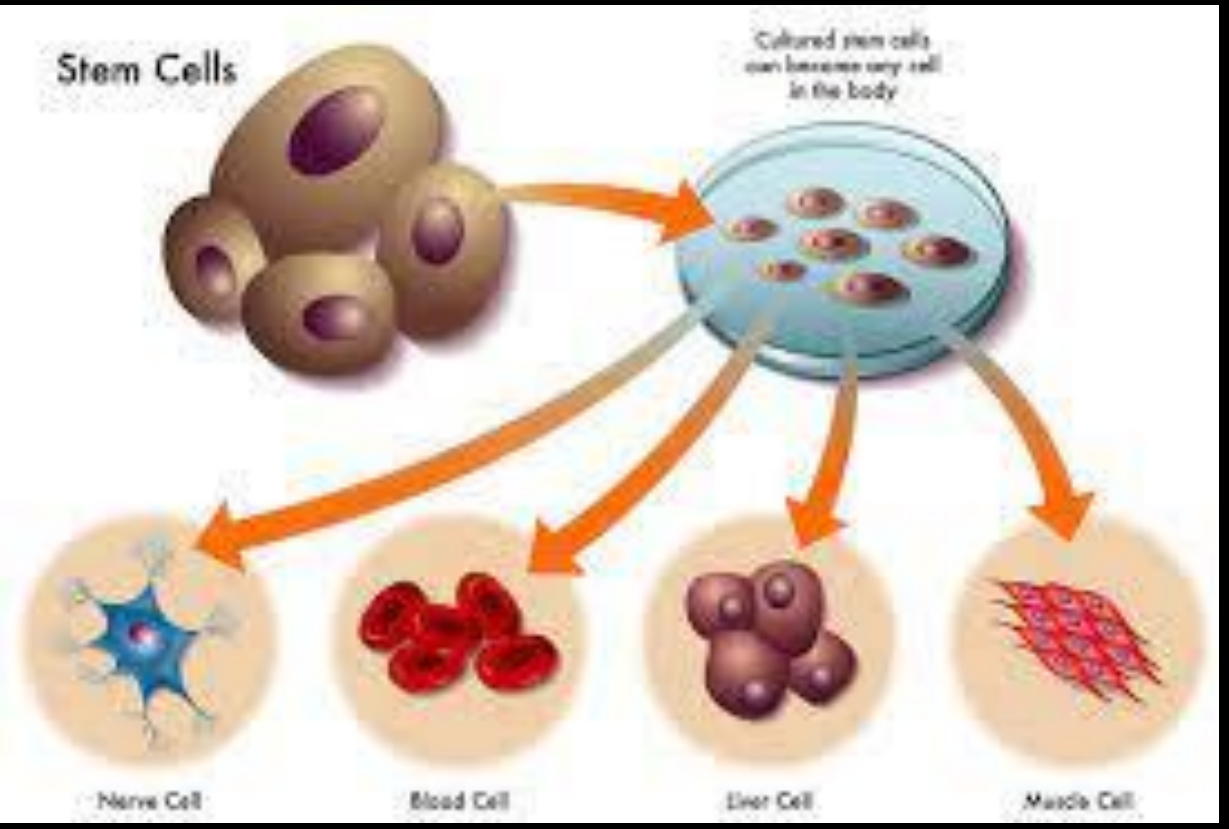


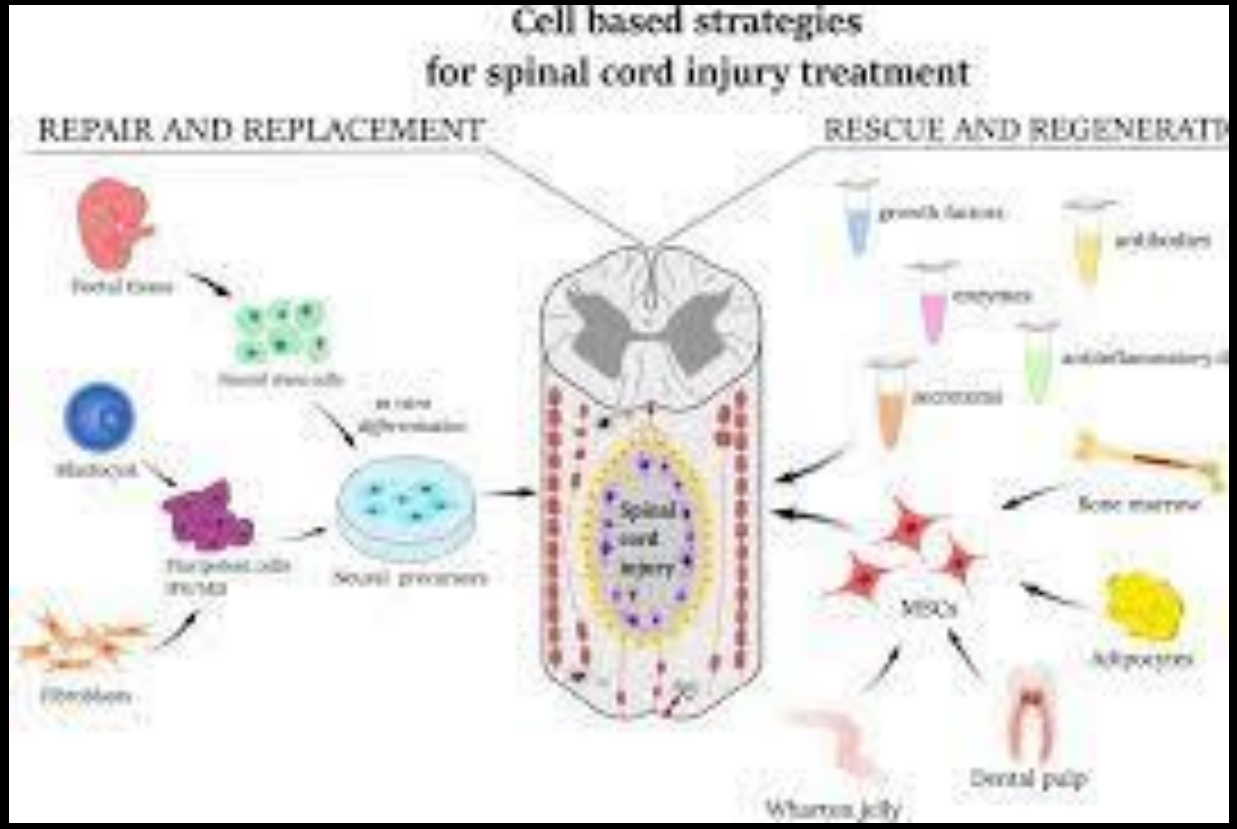
What are the important biological components?

Autologous Controlled Serum (ACS)

- Incubated whole blood
  - significant source of anabolic cytokines such as IL1-Ra, IL-4, IL-10, and TGF-β
  - may induce the production of exosome-containing micro-RNA that drives beneficial epigenetic changes in the target tissue transforming growth factor-ß (TGF-ß)

What are the important biological components?





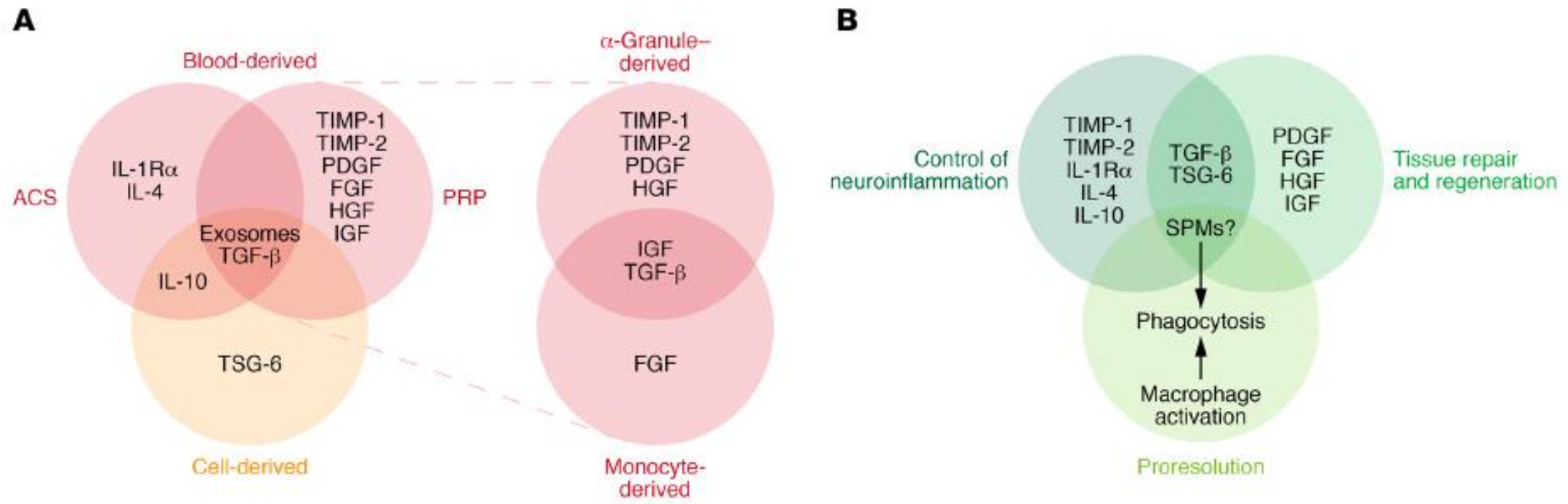
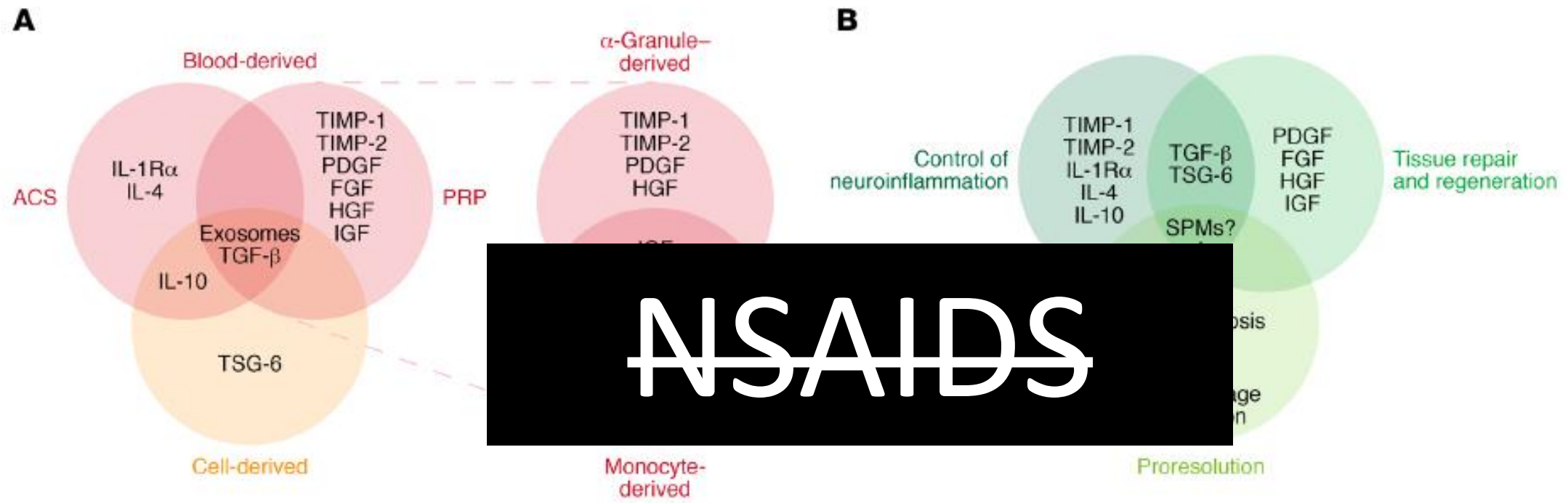


Figure 3. Clinically used blood-derived and cell-derived pain therapies and their mechanisms of action via production of therapeutic mediators. (**A**) PRP contains (a) α-granule–derived growth factors such as PDGF, TGF-β, and HGF, as well as TIMP-1 and TIMP-2 and (b) monocyte-derived factors including TGF-β, FGF, and IGF. ACS provides factors including IL-1 receptor antagonist (IL-1Rα), IL-4, IL-10, and TGF-β. MSCs have been found in clinical treatments to alter macrophage phenotypes, leading to direct and indirect production of IL-10 and TGF-β. MSCs also produce TSG-6 to inhibit inflammation and promote wound healing. Blood- and cell-derived therapies could also contain exosomes.(**B**) Common therapeutic mediators and mechanisms of action include (a) control of neuroinflammation, (b) tissue repair, and (c) pro-resolution processes. Notably, PRP, ACS, and MSCs may also contain or produce SPMs that produce multiple beneficial effects. ACS, autologous conditioned serum; MSC, mesenchymal stromal cells; PRP, platelet-rich plasma; SPM, specialized pro-resolving mediators.



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Animal Studies

Efficacy of intervertebral disc regeneration with stem cells — A systematic review and meta-analysis of animal controlled trials

Zhen Wang [a], Carman M. Perez-Terzic [b,c], Jay Smith [b], William D. Mauck [d], Randy A. Shelerud [b,e], Timothy P. Maus [f], Tai-Hua Yang [g,h], Mohammad Hassan Murad [a], Shanmiao Gou [b,d], Marisa J. Terry [b], Jason P. Dauffenbach [b], Mathew J. Pingree [b,d], Jason S. Eldrige [d], Khaled Mohammed [a], Khalid Benkhadra [a], Andre J. van Wijnen [i], Wenchun Qu [b,d,e,*]

Stem cells transplanted to the IVD in animals decelerate and arrest the IVD degenerative process. Further studies in human clinical trials will be needed to advance our knowledge of the benefit.

Gene 564 (2015) 1–8

Human Studies

Table 3. Preclinical and clinical evidence supporting the use of MSCs for osteoarthritis in knee and hip, tendinopathy, and spine disease

	OA: knee	OA: hip	Tendinopathy	Spine
MSCs	Proposed mechanisms: Therapeutic effects believed to be secondary to (a) paracrine activity and macrophage induction of cytokines such as IL-10 and TGF-β, and (b) potential direct cellular differentiation. MSC sources include bone marrow, adipose, umbilical cord, synovium, and peripheral blood.			
Evidence for clinical effectiveness	RCTs demonstrate effectiveness of MSCs as a stand-alone technique (139) and as part of a surgical procedure (140). Meta-analyses support the effectiveness of both approaches with noted variability of technique and cell sources (89, 143).	Observational and preliminary data support potential therapeutic effect of MSCs for hip arthritis (186, 187).	RCT of MSCs vs. PRP demonstrates short-term advantages of MSCs in Achilles tendinopathy (188). Observational trial of MSC for rotator cuff demonstrated improved symptoms and MRI findings after treatment (189).	Observational data and small randomized trials support the use of MSCs for discogenic pain (156, 190). The use of MSC for spine-related conditions is predominantly as a surgical adjuvant (191).
Laboratory evidence for tissue regeneration	Cartilage growth noted in models using MSCs with surgical scaffold (192, 193) as well as intra-articular injection of culture-expanded cells (194).	Positive evidence of MSC-mediated cartilage regeneration in various OA models (195).	Evidence of MSC differentiation into tenocytes with enhanced tendon strength in rabbit Achilles (196).	Radiographic and histologic evidence of intervertebral disc regeneration in a canine model (197).
Clinical evidence for tissue regeneration	4-year observational trial of BMAC in surgical scaffold demonstrates pain reduction and MRI improvements in cartilage defects (198). Observational trial of intra-articular cultured MSCs demonstrates improvement in pain and function, with MRI evidence of cartilage regeneration (199).	2.5-year observational trial of cultured bone marrow MSCs injected into hip, ankle, or knee demonstrated improved pain and function with MRI evidence of cartilage regrowth in the majority of patients with hip OA (200).	MRI and arthroscopic evidence for tendon regeneration after MSC injection for rotator cuff tears (189).	Observational trials demonstrate some patients have improvement in MRI-assessed disc disease after MSC injection (156, 201).
Comments	Evidence for tissue regeneration/ cellular replacement is stronger with the use of cultured MSCs and surgical scaffolds.	No RCTs for use of MSCs in hip OA.	Limited data for MSC use in tendinopathy.	Limited data for safety and efficacy with intrathecal administration.

Major mechanisms include paracrine activity, production of antiinflammatory mediators and growth factors, and activation of monocytes/macrophages. Tissue regeneration may be a mechanism, especially with the use of culture-expanded cells and surgical scaffolds. BMAC, bone marrow aspirate concentrate; MSCs, mesenchymal stromal cells; OA, osteoarthritis.

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Regenerative Therapies for Spine	Mesenchymal Stem Cells (MSC)
Mechanism	Proposed mechanisms: Therapeutic effects believed to be secondary to (a) paracrine activity and macrophage induction of cytokines such as IL-10 and TGF-β, and (b) potential direct cellular differentiation. MSC sources include bone marrow, adipose, umbilical cord, synovium, and peripheral blood.
Evidence for clinical effectiveness	Observational data and small randomized trials support the use of MSCs for discogenic pain (156, 190). The use of MSC for spine-related conditions is predominantly as a surgical adjuvant (191).
Laboratory evidence for tissue regeneration	Radiographic and histologic evidence of intervertebral disc regeneration in a canine model (197).
Clinical evidence for tissue regeneration	Observational trials demonstrate some patients have improvement in MRI-assessed disc disease after MSC injection (156, 201).
Comments	Limited data for safety and efficacy with intrathecal administration.

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	Bone Marrow Aspirate Concentrate - Autologous							
	Observational Studies							
Pettine 2015	centralized LBP≥6 mos; failed conservative tx≥3 mos; ODI of at least 30/100; VAS of at least 40/100	MRI modified Pfirmann score of 4-7; Modic I or II; disc height loss of <30%	not required, but 7 had discogram to confirm affected levels	VAS	26	26	3,6,12 months	6 months: 19/26 [73% (56-90%)] 12 months: 16/26 [62% (43-80%)]
Wolff 2020			positive discogram	NRS	33	33	2,6,12,24, 52 weeks	As reported: 2 weeks 4/29 (13.8%, 95% CI: 1.2-26.3%) 6 weeks 11/24 (45.8%, 95% CI: 25.6-65.8%) 12 weeks 7/17 (41.1%, 95% CI:17.8-64.6%) 24 weeks 4/17 (23.5%, 95% CI: 3.3-43.7%) 52 weeks 7/18 (38.9%, 95% CI: 16.4-61.4%) Worst Case analysis: 2 weeks 4/33 (12.1%, 95% CI: 1.0-23.3%) 6 weeks 11/33 (33.3%, 95% CI: 17.2-49.4%) 12 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%) 24 weeks 4/33 (12.1%, 95% CI: 1.0-23.3%) 52 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%)
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Kumar 2017	discogenic LBP ≥3 mos; failed conservative tx; ≥4/10 VAS; ≥30% disability ODI	MRI (Pfirmann stages 3 or 4); decrease in disc height of >20%	degenerative symptomatic discs on discography	VAS	10	10	1 week, 1,3,6,9,12 months	4/33 (12.1%, 95% CI: 1.0-23.3%) 52 weeks 7/33 (21.2%, 95% CI: 7.3-35.2%)

Regenerative Therapies for Spine	Autologous conditioned serum (ACS)
Mechanism	Proposed mechanisms: Therapeutic effects are believed to be due to enriched concentrations of anti-inflammatory cytokines such as IL-1Ra, IL-4, and IL-10, growth factors such as TGF-β, and exosomes.
Evidence for clinical effectiveness	RCT demonstrates improvements in radicular pain following epidural injection and superiority to lower dose epidural steroid (182). Other supportive evidence is observational.
Laboratory evidence for tissue regeneration	No published studies investigating the histologic/regenerative impact of ACS on disc or spine pathology.
Clinical evidence for tissue regeneration	No published studies investigating radiographic restoration of disc or spine pathology.
Comments	ACS data are more limited in spine applications.

Office-Based Mesenchymal Stem Cell Therapy for the Treatment of Musculoskeletal Disease: A Systematic Review of Recent Human Studies

Luke Law, MD,* Christine L. Hunt, DO, MS,† Andre J. van Wijnen, PhD,‡,§ Ahmad Nassr, MD,‡ A. Noelle Larson, MD,‡ Jason S. Eldrige, MD,¶ William D. Mauck, MD,¶ Mathew J. Pingree, MD,†,¶ Juan Yang, MD,†,¶ Casey W. Muir, MD,† Patricia J. Erwin, MLS,‖ Mohamad Bydon, MD,‖ and Wenchun Qu, MD, MS, PhD†,¶,**

- *Support in the literature is strongest for the use of bone marrow aspirate concentrate (BMAC) injections for the treatment of knee pain, but applications of the use of BMAC and peripheral blood–derived MSCs for the treatment of hip pain, tendon pain, and disc pain have all been reported.*
- *Further research is required, with large randomized controlled trials.*

Pain Medicine, 20(8), 2019, 1570–1583

The Spine Journal 22 (2022) 226–237

Systematic Review/Meta-Analysis

The effectiveness of intradiscal biologic treatments for discogenic low back pain: a systematic review

Byron J. Schneider, MD[a,*], Christine Hunt, DO[b], Aaron Conger, DO[c], Wenchun Qu, MD, PhD[d], Timothy P. Maus, MD[e], Yakov Vorobeychik, MD, PhD[f], Jianguo Cheng, MD, PhD[g], Belinda Duszynski, BS[h], Zachary L. McCormick, MD[i]

RESULTS

The literature search yielded 3,063 results, 37 studies were identified for full-text review, and 12 met established inclusion criteria for review. **The quality of evidence on effectiveness of intradiscal biologics was very low.** A single randomized controlled trial evaluating platelet-rich plasma reported positive outcomes but had significant methodological flaws. A single trial that evaluated mesenchymal stem cells was negative. Success rates for platelet-rich plasma injectate in aggregate were 54.8% (95% Confidence Interval: 40%–70%). For mesenchymal stem cells, the aggregate success rate at six months was 53.5% (95% Confidence Interval: 38.6%–68.4%), though using worst-case analysis this decreased to 40.7% (95% Confidence Interval: 28.1%–53.2%). Similarly, ≥30% functional improvement was achieved in 74.3% (95% Confidence Interval: 59.8%–88.7%) at six months but using worst-case analysis, this decreased to 44.1% (95% Confidence Interval: 28.1%–53.2%).

CONCLUSION

Limited observational data support the use of intradiscal biologic agents for the treatment of discogenic low back pain. According to the Grades of Recommendation, Assessment, Development and Evaluation System, the evidence supporting use of intradiscal mesenchymal stem cells and platelet-rich plasma is very low quality.

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CONCLUSION: Limited observational data support the use of intradiscal biologic agents for the treatment of discogenic low back pain. According to the Grades of Recommendation, Assessment, Development and Evaluation System, the evidence supporting use of intradiscal mesenchymal stem cells and platelet-rich plasma is very low quality.

Regenerative Medicine for Axial and Radicular Spine-Related Pain: A Narrative Review

Desai M, et al. Pain Practice. 2020

Conclusions: Level I studies to support:

- Use of PRP and MSC injections for discogenic pain
- PRP for facet joint injections with PRP
- Epidural injections of autologous conditioned serum and epidural prolotherapy
- PRP and prolotherapy for sacroiliac joint pain.
- One level I study showed that facet joint prolotherapy has no significant benefit.
- **Notably, no intervention has multiple published level I studies.**

Guidelines

Pain Physician 2019; 22:S1-S74 • ISSN 1533-3159

Guidelines

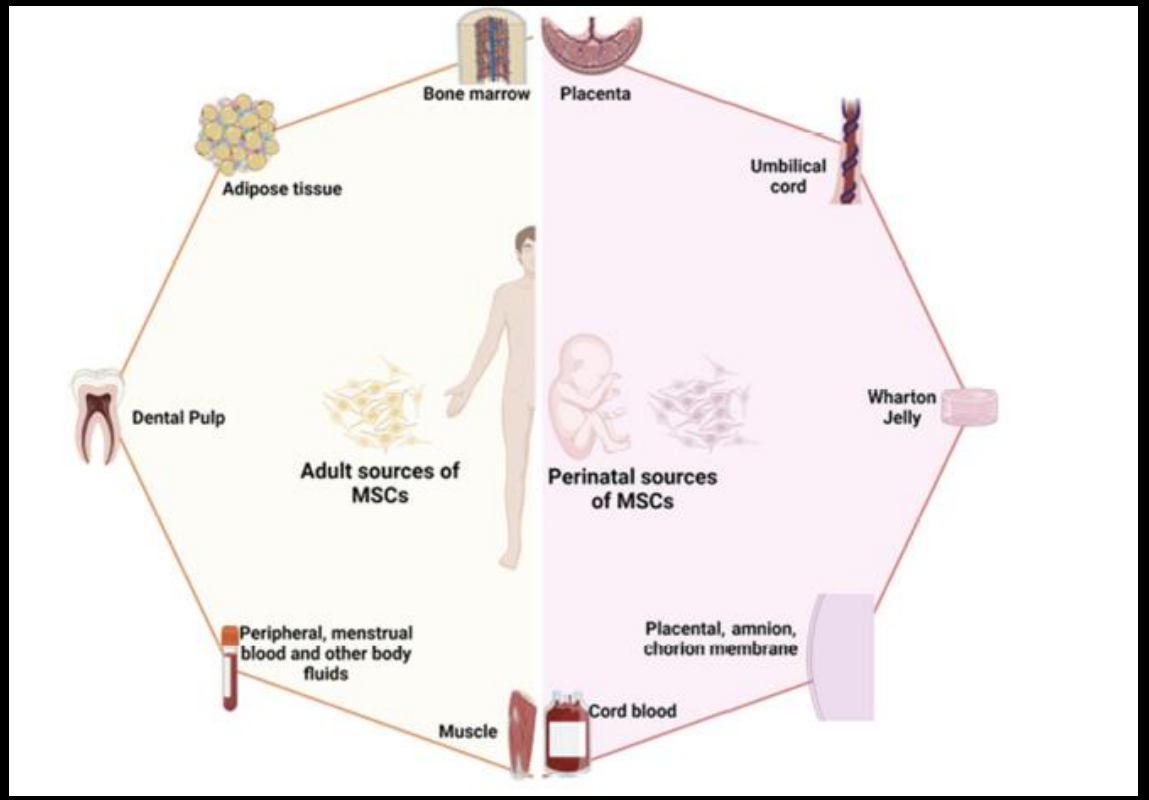
Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines

Annu Navani, MD[1], Laxmaiah Manchikanti, MD[2], Sheri L. Albers, DO[3], Richard E. Latchaw, MD[4], Jaya Sanapati, MD[5], Alan D. Kaye, MD, PhD[6], Sairam Atluri, MD[7],Sheldon Jordan, MD[8], Ashim Gupta, PhD, MBA[9], David Cedeno, PhD[10], Alejandro Vallejo, BS[11], Bert Fellows, MA[12], Nebojsa Nick Knezevic, MD, PhD[13], Miguel Pappolla, MD[14], Sudhir Diwan, MD[15], Andrea M. Trescot, MD[16], Amol Soin, MD[17], Adam M. Kaye, PharmD, FASCP, FCPhA[18], Steve M. Aydin, DO[19], Aaron K. Calodney, MD[20], Kenneth D. Candido, MD[21], Sanjay Bakshi, MD[22], Ramsin M. Benyamin, MD[23], Ricardo Vallejo, MD, PhD[24], Art Watanabe, MD[25], Douglas Beall, MD[26], Todd P. Stitik, MD[27], Patrick M. Foye, MD[28], Erik M. Helander, MBBS[29], and Joshua A. Hirsch, MD[30]

Conclusion: Based on the evidence synthesis summarized above, there is Level III evidence for intradiscal injections of PRP and MSCs, whereas the evidence is considered Level IV for lumbar facet joint, lumbar epidural, and sacroiliac joint injections of PRP, (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

Evidence-Based Clinical Practice Guidelines on Regenerative Medicine Treatment for Chronic Pain: A Consensus Report from a Multispecialty Working Group

D'Souza, et al. Journal of Pain Research 2024:17 2951–



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D'Souza, et al. Journal of Pain Research 2024:17 2951–

Consensus Point 1. Patients should be advised that the mechanisms of action of injectable biologics in the treatment of chronic pain conditions are multifaceted and related to the specific injected biologic agent. Most mechanisms are centered on modulation of the injected tissue to promote an anti-inflammatory microenvironment. Common mechanisms include:

(1) release of anti-inflammatory cytokines,
(2) release of growth factors
(3) differentiation of mononuclear cells into anti-inflammatory macrophages
(4) release of extracellular vesicles that bind to target tissue resident cells and perform a paracrine function similar to progenitor cells.

Evidence-Based Clinical Practice Guidelines on Regenerative Medicine Treatment for Chronic Pain: A Consensus Report from a Multispecialty Working Group

Consensus Point 26. The current evidence suggests that intra-discal BMAC injection may provide long-term alleviation of pain and improvement in physical function for patients with discogenic pain, although these differences may be similar to those with intra-discal injection with PRP (Level I, Grade C).

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Consensus Point 26. The current evidence suggests that intra-discal BMAC injection may provide long-term alleviation of pain and improvement in physical function for patients with discogenic pain, although these differences may be similar to those with intra-discal injection with PRP (Level I, Grade C).

Consensus Point 39. It is recommended that all NSAIDs, including aspirin, are held for four to five times their respective plasma half-lives (eg, seven days for aspirin) prior to scheduling a procedure involving injectable biologics. These medications should continue to be held post-procedurally given the rapid onset of these agents, as even one dose can impact platelet aggregation and growth factor release. We recommend a hold of at least four to eight weeks, which corresponds to the peak effect of injectable agents (Level II-2, Grade B).

Consensus Point 46. While topical infiltration of local anesthetic is reasonable during procedures, avoidance of local anesthetic directly at the final site of injection is recommended as this can be cytotoxic to the biologic injectate. In vitro studies suggest that ropivacaine is the least cytotoxic, although additional studies are warranted to confirm this finding (Level II-2, Grade B).

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Consensus Point 37. Culture expansion of MSCs falls under Section 351 of the Federal Public Health Service Act. Cellular and tissue-based products, such as MSCs, cannot legally undergo cultural expansion as doing so represents more than minimal manipulation (Level N/A, Grade A).

Consensus Point 49. Injectable biologics, notably PRP and MSCs, have been shown to be a safe treatment modality with minimal adverse effects related to the injection (localized soreness, bruising, infection, bleeding). Severe adverse reactions are very rare and may consist of neoplasm formation, disease transmission, reactivation of latent viruses, and graft-versus-host disease (Level I, Grade B).

D'Souza, et al. Journal of Pain Research 2024:17 2951–

Evidence-Based Clinical Practice Guidelines on Regenerative Medicine Treatment for Chronic Pain: A Consensus Report from a Multispecialty Working Group

- In well-selected individuals with certain chronic pain indications, use of injectable biologics may provide superior analgesia, functionality, and/or quality of life compared to conventional medical management or placebo.
- Future high-quality randomized clinical trials are warranted with implementation of minimum reporting standards, standardization of preparation protocols, investigation of dose–response associations, and comparative analysis between different injectable biologics.

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Conclusions

- Evolving knowledge of mechanisms of action of biological agents
- Limited evidence for spinal use of PRP, MSCs, ACS-limited follow-up beyond 6 months
- More controlled studies needed to assess response and risks with treatment, especially long-term
  - Minimal additional risks reported beyond the risks associated with underlying procedure
- Patients should be fully informed of known risks/benefits and off-label use and often high out of pocket costs